REMARKS

Upon entry of the present amendment, claims 1-9, 11-14, and 16 are canceled, claims 10, 15 and 23 are amended, and new claim 24 is added. Accordingly, claims 10, 15, and 17-24 are presently pending. All claims are directed to the invention of Group I elected in connection with the restriction requirement of November 13, 2007.

In an effort to expedite prosecution, Applicants have canceled non-elected claims 11-14 and amended independent claim 15 to more clearly specify that the composition at issue is a medicament for allergen-specific immunotherapy that is capable of inducing strong antibody responses with less granulomatous tissue reactions, the medicament containing a therapeutically effective amount of microparticles in a pharmaceutical formulation, the microparticles consisting essentially of:

(a) a bead consisting of three-dimensionally cross-linked agarose; and

(b) a purified recombinant polypeptide allergen derived from plant pollen bound to said bead by means of a covalent bond between said cross-linked agarose and a reactive group of said allergen.

To further expedite prosecution, dependent claim 23 has also been amended to specify that the three-dimensionally cross-linked agarose bead consists essentially of cyanogen bromide-activated spherical agarose and the purified recombinant polypeptide allergen derived from plant pollen consists essentially of the timothy grass pollen allergen Phl p 5b of SEQ ID NO:1. New claim 24 further defines the pharmaceutical formulation as an injectable solution (such as a parenteral solution – claim 10), rectal foam, nasal spray, ointment or plaster.

Support for these amendments is found in the specification as originally filed, as evidenced by the following excerpts from the published application, US-2005-0095298 published May 5, 2005:

- "The coupling of the carbohydrate-based beads to the antigen is based on the principle of forming *a covalent bond between the carbohydrate backbone of the bead and a reactive*

group of the antigen." – paragraph [0012], emphasis added;

- "It has been found that the microparticles of the present invention elicited comparable immune responses *but less granulomatous tissue reactions* than aluminium hydroxide." – paragraph [0016], emphasis added;
- "Such a medicament can be administered *nasally, rectally or preferably parenterally*. The microparticles can be included in *suitable pharmaceutical formulations like solutions for injection, rectal foams or nasal sprays*. It is also possible to prepare suitable *ointments or plasters*." – paragraph [0017], emphasis added;
- "The experiments show that purified rPhl p 5b allergen which is covalently bound to the carbohydrate-based bead *induced strong IgG1, IgG2a/b and IgG3 antibody responses* in mice." – paragraph [0018], emphasis added;
- "It can be concluded from the experiments which show that the *cytokine response is much more vigorous* in the group treated with microparticles of the present invention compared to the control group wherein the antigen was absorbed to aluminium *that the cellular immune response is stimulated*." – paragraph [0021] , emphasis added;
- "[T]he experiments. . .show that the immunisation of mice with the microparticles of the present invention *induced less granulomatous reactions* than the use of aluminium hydroxide under comparable treatment." – paragraph [0023] , emphasis added;
- Example 2, paragraphs [0049] to [0051], entitled "Mice Immunized with CBP-Bound rPhl p 5b Show Strong Cytokine Responses to Timothy Grass Pollen Extract" wherein the medicaments of the present invention are shown to mount "*significantly stronger cytokine production*"; and
- Example 3, paragraphs [0052] to [0054], entitled "CBP-Bound rPhl p 5b Induces Less Granulomatous Tissue Reaction than Alum-Adsorbed Allergen" wherein medicaments of the present invention are shown to induce relatively small "inflammatory tissue reactions" containing "less granular debris".

Thus, Applicants respectfully submit that no new matter has been added. However, Applicants reiterate that these amendment are presented solely for the purpose of expediting prosecution and should not be construed as Applicants' agreement with or acquiescence to the grounds of rejection previously set forth.

Pursuant to the Final Office Action of October 30, 2008, elected claims 10, 15, and 17-23 stand finally rejected on both reference grounds (namely, anticipation and/or obviousness) and non-reference grounds (namely, enablement and written description). Applicants respectfully submit that the instant response renders moot the outstanding claim rejections and places the instant application in condition for allowance. Further to this position, Applicants submit the following remarks:

Rejections Under 35 USC 112, First Paragraph

Claims 10, 15 and 17-23 stand finally rejected under 35 U.S.C. § 112, first paragraph, for failing to comply with the enablement and written description requirements. While the Examiner finds the specification to describe and enable a "microparticle consisting essentially of Phl p 5b covalently bound to CBP[1]", she continues to find the following aspects to lack adequate support:

(a) medicaments for allergen-specific immunotherapy *capable of generating an immunoprotective response* (claim 15);

(b) beads consisting essentially of *any* three dimensionally cross-linked carbohydrate of any variety (claim 15), including one consisting essentially of agarose (claim 16) or comprising cyanogen bromide-activated spherical agarose (claim 23); and

(c) polypeptide allergens derived from *any* plant pollen (claim 15), *any* grass pollen (claim 18), including one derived from timothy grass pollen (claim 19) or comprising the timothy grass pollen allergen Phl p 5b of SEQ ID NO: 1 (claim 23);

[1] Here and elsewhere, the Examiner erroneously interprets the abbreviation "CBP" as referring exclusively to cyanogen bromide-activated spherical Sepharose particles. However, both in the instant specification and in Applicant's own publications (Gronlund et al., Immunology 2002, and Neimart-Andersson et al., Allergy 2008) the term "CBP" is expressly defined as referring to "carbohydrate-based particles".

(d) microparticles of *any* size, including those ranging from 0.1 to 10 μm (claim 21) and from 0.5 to 5 μm (claim 22).

The Examiner's central position seems to be that Applicants' have not adequately disclosed and enabled the generation of an ***immunoprotective*** response. Applicants respectfully disagree with this conclusion for reasons of record. However, Applicants note that the Examiner admits at p. 6 of the outstanding final office action that both the "art of Gronlund et al." (Gronlund et al., Immunology, 2002) and the instant specification teach that "CBP can be used as an adjuvant in place of Alum because it generates increased antibody any [sic] cytokine production over alum without the formation of granulomatous tissue reaction". Thus, in an effort to expedite prosecution, Applicants have canceled reference to "generating an immunoprotective response" in favor of medicaments capable of "inducing strong antibody responses with less granulomatous tissue reactions". Applicants respectfully submit that experimental results presented herein (e.g., Examples 2 and 3) conclusively demonstrate that microparticles of the present invention, i.e., microparticles consisting of a three-dimensionally cross-linked agarose bead having a purified recombinant polypeptide plant pollen allergen covalently bound thereto, are capable of stimulating the production of antibodies like their conventional alum counterparts but without the granulomatous tissue reactions associated therewith.

As mentioned previously, the medicaments of the present invention operate in a manner analogous to conventional Alum-adsorbed allergy vaccines by inducing allergen-specific IgG responses similar to those of Alum-based particles[2]. Accordingly, one of ordinary skill in the art would be well versed in the methods of making and using the medicaments of the present invention, without undue experimentation and with predictable results. Furthermore, Applicants have conclusively demonstrated herein that the microparticles of the present invention are capable of inducing strong IgG1, IgG2a/b, and IgG3 antibody responses in mice, antibodies

[2] See e.g., Vrtala et al., *J. Immunol.*, 2000, 165:6653-9, and 1998, 160:6137-40, and, referenced in the instant specification at pp. 8 and 9, respectively.

referred to in the art as "blocking antibodies" for their ability to prevent contact between the allergen and the IgE molecules present in the allergic patient's body, thereby avoiding mast cell- and basophil-mediated allergic responses such as cytokine secretion and histamine release,[3] with minimal negative side effects (like the granulomatous tissue reaction), with predictable efficacy of adsorption, with predictable stability of adsorbents, and without altering the functionality of the bound allergen. Thus, it is readily apparent that the medicaments of the instant invention are suited to allergen-specific immunotherapy and are capable of "inducing strong antibody responses with less granulomatous tissue reactions" as the pending claims now require. Thus, Applicants respectfully submit that the scope of the pending claims is commensurate with the admitted scope of enablement. Applicants further submit that the remaining allegations of undue unpredictability and criticality fall with this primary one. Accordingly, Applicants respectfully request reconsideration and withdrawal of the enablement rejection.

With regard to the remaining issues of items (b) – (d), Applicants reiterate that the present invention relates to the discovery of the advantageous nature of carbohydrate-based allergen particles (CBPs) over traditional metal-based allergen particles (like aluminum hydroxide and iron oxide particles) in the context of allergen-specific immunotherapy. Applicants respectfully submit that this novel finding is not restricted to a specific carbohydrate or specific polypeptide allergen or even a specific size range. Contrary to the Examiner's suggestion, the improved "allergen specific non-responsiveness" and "high density" coupling associated with the medicaments of the present invention and observed by Neimert-Andersson et al. in the Allergy, 2008 reference arises more from the selection of carbohydrate over metal and covalent binding over chemical adsorption that any other factor.

Applicants further submit that the principle mode of allergen-specific immunotherapy does not depend on the nature of the particular allergen but can be readily and routinely generalized for other peptide allergens. In addition, as noted in the instant specification and in the prior responses, the covalent coupling of purified recombinant polypeptide allergens to

[3] See Ball et al., *Eur. J. Immunol.*, 1999 29:2026-36 and van Neerven et al., *J. Immunol.*, 1999, 163: 2944-52, reference numbers 28 and 29, respectively, of the Gronlund publication discussed in detail in the previous response, which serves as the basis for the instant application.

carbohydrate-based particles, such as agarose/sepharose beads, uses well-described and reproducible procedures analogous to those conventional in the art of ELISA-based diagnostic protocols. Thus, in the context of the instant invention, the timothy grass pollen allergen Phl p 5b (SEQ ID NO:1) is indeed representative of the requisite structural and functional properties of the genus of "purified recombinant polypeptide allergens derived from plant pollen". As for the supporting carbohydrate bead, to expedite prosecution, Applicants have amended the claims to require the bead to consist of three-dimensionally cross-linked agarose. Thus, Applicants respectfully submit that the claimed genus of microparticles is adequately described and enabled by the teachings of the instant specification coupled with the knowledge in the art.

In sum, Applicants respectfully submit that the *in vitro* and *in vivo* data presented in the instant specification demonstrate that a reasonable correlation exists between the scope of the claims and the scope of enablement. Accordingly, Applicants submit that one of ordinary skill in the art would be able to practice the invention of the claims 10 and 15-23 without undue experimentation and with a reasonable expectation of success. Applicants further submit that the instant specification provides an adequate written description of the genus of medicaments encompassed by claims 10, 15, and 17-24, so as to convey with reasonable clarity to those skilled in the art that, as of the filing date sought, Applicants were in possession of the invention now claimed. Accordingly, Applicants respectfully petition for the reconsideration and withdrawal of the outstanding rejections under 35 U.S.C. § 112, first paragraph.

Rejections Under 35 USC 102

Gronlund:

Claims 10 and 15-23 stand rejected under 35 U.S.C. § 102(a) as being anticipated by Gronlund et al. (*Immunology*, 2002).

Applicants direct the Examiner's attention to Applicant's Exhibit One which contains the PubMed citation and abstract for the Gronlund et al. (*Immunology*, 2002) reference. Applicants respectfully submit that when one compares the actual publication date of the Gronlund reference (December 2002) with Applicant's priority date (April 2002), one

realizes that the Gronlund reference cited by the Examiner is not, in fact, prior art under any subsection of 35 U.S.C. § 102 and therefore cannot be used to anticipate the invention of the pending claims. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection in view of Gronlund et al.

Nordvall, King and van Toorenbergen:

Claims 1-6, 9, and 10 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Nordvall et al. (*Allergy*, 1986); claims 1-3, 5-6, and 9-10 stand rejected under 35 U.S.C. § 102(b) as being anticipated by King et al. (*Clinical Allergy*, 1976); and claims 1-2, 5-6, and 9-10 stand rejected under 35 U.S.C. § 102(b) as being anticipated by van Toorenbergen et al. (*International Archives of Allergy and Immunology*, 2000).

Applicants respectfully submit that these rejections are rendered moot by the instant amendments to claim 15. However, in the event the Examiner finds the above concerns to extend to claims 10, 15 and 17-24 as presently pending, Applicants offer the following comments:

As mentioned previously, the disclosures of Nordvall, King and van Toorenbergen are limited to the diagnostic use of particle bound allergens, i.e., the use of bead-bound allergens to measure allergen specific antibodies for diagnostic purposes. However, none disclose or suggest a medicament formulated for pharmaceutical administration (e.g., as a parenteral solution, rectal foam, nasal spray, ointment or plaster) for allergen-specific immunotherapy that is capable of inducing strong antibody responses with less granulomatous tissue reactions, the medicament containing a therapeutically effective amount of microparticles consisting essentially of: (a) a bead consisting of three-dimensionally cross-linked agarose; and (b) a purified recombinant polypeptide allergen derived from plant pollen bound to said bead by means of a covalent bond between said cross-linked agarose and a reactive group of said allergen.

In contrast, van Toorenbergen et al. utilize a crude extract of whole plant stamen incubated in a coupling buffer, with the resulting allergen beads then suspended in a RAST

buffer for use in antibody binding studies. In a similar fashion, King et al. describe a grass pollen allergen concentrate as the source of allergen, with the resulting allergen beads then suspended and stored in 0.1M borate/1 M NaCl, pH 8.0 for basophil immune adherence tests. Finally, Nordvall et al. utilize a "partially purified timothy pollen preparation" bound to Sepharose bead via a protein-A/biotin linkage for use in the context of a sandwich-type ELISA (see p. 577-578, legend to Figure 5). Thus, it is readily apparent that none of the cited prior art combine a purified, recombinant polypeptide plant pollen allergen bound to a three-dimensionally cross-linked agarose bead by means of a covalent bond between the agarose bead and a reactive group of said allergen with a pharmaceutical formulation to yield a medicament for allergen-specific immunotherapy capable of inducing strong antibody and cytokine responses with less granulomatous tissue reactions.

Further to this position, Applicants direct the Examiner's attention to Exhibits Two and Three, references to Pauli (Pauli, Gabrielle et al., J. Allergy Clin. Immunol., vol. 122 (5): 951-960, November 2008) and Himly (Himly, Martin et al., FASEB J., 10.1096, November 15, 2002). According to Pauli et al., recombinant antigens are vastly superior to purified natural antigens, particularly in the context of human immunization. See, for example, p. 951, col. 2 ("One method for improving allergen-specific immunotherapy is to use recombinant allergens produced by DNA technology"). See also p. 959, col. 1 ("this study demonstrates that a recombinant allergy. . .vaccine can be produced with a high level of purity and reproducibility. . .and has a number of advantages over treatment with a complex allergen source, including the avoidance of unnecessary induction of IgE against new components"). Himly concurs, noting that while plant-based expression systems might be the choice for the production of allergens for diagnostic purposes, genetically engineered allergens having reduced IgE binding epitopes (hypoallergens), reduced risk of IgE-mediated side effects, and improved T cell recognition are preferable for specific immunotherapy (SIT). See p. 2, col. 2.

Thus, Applicants respectfully submit that none of the cited prior art embodiments, all of which utilize crude whole pollen extracts, would be suitable for "allergen-specific

immunotherapy" and capable of "inducing strong antibody and cytokine responses with less granulomatous tissue reactions" as the pending claims require. Accordingly, in that none of Nordvall et al., King et al. and van Toorenbergen et al. disclose each and every element of the pending claims as amended herewith, they cannot serve to anticipate the invention of claims 10, 15 and 17-24 as presented herein. Thus, Applicants respectfully request reconsideration and withdrawal of the outstanding rejections.

Rejection under 35 USC 103

van Toorenbergen & Nordvall:

Claims 15, 18, and 19 stand rejected under 35 U.S.C. § 103(a) as being obvious over van Toorenbergen et al. in view of Nordvall et al.

In order to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

The deficiencies and limitations of Nordvall and van Toorenbergen with respect to the anticipation of claim 15 discussed above are equally applicable to the allegation of obviousness. Applicants respectfully submit that even if one were to combine the teachings as proposed, one would not arrive at the invention of the pending claims, namely an administrable medicament formulated for pharmaceutical administration for allergen-specific immunotherapy capable of inducing strong antibody responses with less granulomatous tissue reactions containing a therapeutically effective amount of microparticles in a pharmaceutical formulation, the microparticles consisting essentially of:

(c) a bead consisting of three-dimensionally cross-linked agarose; and

(d) a purified recombinant polypeptide allergen derived from plant pollen bound to said bead by means of a covalent bond between said cross-linked agarose

and a reactive group of said allergen.

Thus, in that neither van Toorenbergen et al. nor Nordvall et al., neither alone nor in combination, teach or suggest all the limitations of the pending claims as amended herewith, they cannot together serve to render obvious the invention of claims 15, 18, and 19 as presented herein. Accordingly, Applicants respectfully request reconsideration and withdrawal of the outstanding rejection.

van Toorenbergen, Nordvall or King & Kovacsovics-Bankowski:

Claims 15, 21, and 22 stand further rejected under 35 U.S.C. § 103(a) as being obvious over van Toorenbergen et al., Nordvall et al., or King et al., each in view of Kovacsovics-Bankowski et al. (*European Journal of Pharmaceutics and Biopharmaceutics*, 2000).

The limitations of Nordvall et al., King et al., and van Toorenbergen et al. are discussed above. Applicants respectfully submit that not only does Kovacsovics-Bankowski et al. fail to cure the above-noted deficiencies but in fact presents a number of its own deficiencies. In order to establish a *prima facie* case of obviousness, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. In this case, Applicants respectfully submit that one of skill in the art would not consider the disclosures to be sufficiently analogous to warrant combination. In particular, Kovacsovics-Bankowski utilizes microspheres made from a totally different material (i.e., iron oxide beads as opposed to sepharose/agarose beads), utilized for a totally different purpose (i.e., therapeutic antigen presentation as opposed to diagnostic antibody binding). Given the divergent nature of the use to which each is adapted, Applicants respectfully submit that one of ordinary skill in the art would not have been motivated to scale down the diagnostic particles of van Toorenbergen, Nordvall or King to the therapeutically beneficial sizes proposed by Kovacsovics-Bankowski. Nor would one of ordinary skill in the art been

motivated to pharmaceutically formulate and therapeutically administer the diagnostic particles of van Toorenbergen, Nordvall or King as taught by Kovacsovics-Bankowski.

It is well settled that if a proposed modification renders a prior art invention being modified unsatisfactory for its intended purpose, then there can be no suggestion or motivation to make the proposed modification (i.e., modification is not obvious). By the same token, if a proposed modification or combination of the prior art changes the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims *prima facie* obvious. See M.P.E.P § 2143.01. In this case, scaling down the particle size of conventional diagnostic beads, typically on the order of 45 to 165 microns,[4] one to three orders of magnitude to 0.5 to 10 micron range disclosed by Kovacsovics-Bankowski constitutes a significant difference that not only would not be routine but would also be expected to impact the operability of the prior art particles in the context of their use in connection with conventional binding assays and the like.

It is further well-settled that even a *prima facie* case of obviousness may be rebutted by so-called "indicia of non-obviousness", e.g., evidence of secondary considerations such as unexpected results, commercial success, long felt but unsolved needs, failure of others, etc. In particular, evidence that a claimed invention yields improved properties or properties not present in the prior art and/or evidence that the claimed invention possesses unexpected properties is generally sufficient to overcome a *prima facie* case of obviousness. See *In re Dillon*, 919 F.2d 688 at 692-93, 16 USPQ2d 1901 (Fed. Cir. 1990); *In re Albrecht*, 514 F.2d 1389, 1396, 185 USPQ 585, 590 (CCPA 1975).

In the context of the instant invention, Applicants have repeatedly shown that their carbohydrate-based allergen particles (CBPs) are vastly superior to traditional metal-based particles in the context of allergen-specific immunotherapy, both in terms of their ability to induce strong antibody and cytokine responses, including the stimulation of therapeutically beneficial blocking antibodies, but also in their avoidance of the granulomatous tissue

[4] See Applicants Exhibit Four - the product specification sheet for Sepharose Protein A beads available through Rockland Immunochemicals, Inc. (Gilbertsville, PA).

reaction characteristic of conventional metal-based particle formulations. To that end, Applicants again direct the Examiner's attention to the findings of comparative Examples 2 and 3 (e.g., "From the data it can be concluded that spleen cells from mice which had received CBP-conjugated rPhl p 5b mounted significantly stronger cytokine production (IFN-.gamma., IL-5) than spleen cells from mice treated with Alum-adsorbed rPhl p 5b.").

Thus, Applicants respectfully submit that instantly claimed invention is not the result an obvious combination but rather a patentable invention having unexpectedly improved properties as compared to the prior art. Accordingly, Applicants respectfully request the Examiner reconsider her assertion of obviousness in view of the surprising and substantial superiority of the instantly claimed carbohydrate-based microparticles.

CONCLUSION

The outstanding Office Action set a three-month shortened statutory period for response, response being due on or before **January 30, 2009**. In that the Petition for a One-Month Extension of Time extends this deadline to on or before **March 2, 2009** (February 28th being a Saturday), Applicants respectfully submit that this response is timely and no additional fee is required. However, in the event that further fees are required to enter the instant response and/or maintain the pendency of this application, the Commissioner is authorized to charge such fees to our Deposit Account No. 50-2101.

If the Examiner has any questions or concerns regarding this communication, she is invited to contact the undersigned.

Respectfully submitted,

Date: March 2, 2009

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